Development of Cellular Therapies for Retinal Disease

Grant Award Details

Development of Cellular Therapies for Retinal Disease

Grant Type: Research Leadership

Grant Number: LA1-02086

Project Objective: To develop therapies for regeneration of the diseased eye with particular focus on macular degeneration, diabetic retinopathy, and retinitis pigmentosa.
1.Determine the detailed molecular mechanisms that both initiate and lead to the establishment of a perpetual state of RPE wound response.
2.Translate the information gained from these cell culture models to direct analysis of AMD tissue to further assess the hypothesis that AMD is fundamentally a disorder of aberrant, runaway wound response.
1)Sustained Subconfluent Culture is Accompanied by Profound Changes in Gene Expression
(the above information was derived from the submitted grant proposal)

Investigator:

Name:	Peter Coffey
Institution:	University of California, Santa Barbara
Type:	PI

Disease Focus: Vision Loss

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: iPS Cell

Award Value: $4,662,366

Status: Active

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: Year 5

View Report

Reporting Period: Year 6

View Report

Grant Application Details

Application Title: Development of Cellular Therapies for Retinal Disease

Public Abstract: The long term goal of our research program is regeneration of the diseased eye. Age-related macular degeneration, diabetic retinopathy, and retinitis pigmentosa are leading causes of blindness for which there are no effective treatments for the majority of cases. Loss of vision is due to progressive degeneration of the photoreceptor cells, or loss of cells that support the photoreceptors, such as retinal pigment epithelial (RPE) cells or cells in the retinal blood vessels. The RPE is a pigmented cell layer that lies just behind the retinal and is necessary for photoreceptor survival. One possible strategy for treatment of these blinding diseases is to replace cells that are lost via transplantation. My work explores this approach, with the object of first identifying and characterizing sources of cells, determining the optimal parameters for transplantation, and investigating molecular, cellular and behavioral events that occur upon transplantation in animal models of retinal degeneration. In the case of age-related macular degeneration, there is a solid body of evidence that RPE cell loss is often an early event in disease progression. We have shown that RPE can be derived from human embryonic stem cells (hESC) and induced pluripotent stem cells (iPSC), and they can rescue vision in rodent and pig models of retinal dystrophy. We have joined forces with interdisciplinary teams in the UK and California to transition this work to the clinic, using RPE derived from hESC. We will also investigate other forms of RPE-based eye disease by generating iPSC from patients, differentiating them to RPE, and analyzing function. Small molecules that are candidate drugs will then be screened for functional rescue. In the case of diabetic retinopathy, we are investigating a strategy to used hESC-derived cells to repair blood vessels. Finally, in retinitis pigmentosa, we will pursue a possible route to replace photoreceptors by converting the surviving retinal ganglion cells into light sensing cells. The aim of the proposed studies is to provide foundational knowledge that will enable and guide further translation of cellular therapies to improve vision in patients.

Statement of Benefit to California:

Age-related macular degeneration (AMD), retinitis pigmentosa (RP) and diabetic retinopathy are leading causes of vision loss and blindness. Because California is the most populous state in the nation, and because the elderly constitute a greater percentage of its population, it is estimated that over 450,000 of Californians will suffer from AMD with severe vision impairment by 2020, leading to huge costs. Diabetes continues to be a major health concern, with vision loss a common outcome. Moreover, the devastating consequences of vision deficits include the progressive loss of independence and productivity, and increased risks of falls, fractures, and depression among diseased population. So this is not only a problem of the individual quality of life, but also an issue of increasing public health burden and concern. Clearly, there is a need for better treatments.

In these diseases, loss of vision is due to progressive degeneration of the light sensitive photoreceptor cells of the eye or defects in the supporting cells of the eye, including the retinal pigmented epithelium (RPE). There is now a solid body of evidence that suggests that RPE degeneration is the first step in AMD. There is no cure for these conditions at present, although studies of model experimental animals, mostly rats and mice, suggest several possible routes to therapy. One of these involves the transplantation of cells to slow the degeneration of photoreceptors by replacing key support cells lost during degeneration. My work explores this approach with the object of first identifying and characterizing sources of ocular cells, determining the optimal parameters for transplantation, and identifying molecular and cellular and behavioral events that occur upon transplantation in animal models of retinal degeneration. One source of cells for transplantation is ocular cells derived from human embryonic stem cells (hESC) or induced pluripotent stem cells (iPSC). We have shown that ocular cells, especially RPE, can be derived from both hESC and iPSC, and they can rescue visual function in rodent models of retinal dystrophy. We have shown that RPE can be derived from both hESC and iPSC, and they can rescue visual function in rodent models of retinal dystrophy. We have teamed up with an interdisciplinary disease team of stem cell biologists, materials chemists, neuroscientists, and retinal surgeons to transition this work towards clinical application for AMD, using hESC to produce RPE. Other research aims are to generate specific blood vessel cells from stem cells to replenish the retinal blood vessels in diabetic retinopathy, to generate new photosensitive cells to restore vision, and to use iPSC derived from patients to understand retinal disease and identify novel treatments. California patients with vision loss will benefit greatly from the studies proposed.

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